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REVIEW ARTICLE

Nose-to-brain delivery of insulin nanoparticles for diabetes management: A review

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ABSTRACT

Hyperglycemia and the onset of insulin resistance or deficiency, or both, are the hallmarks of the group of diseases known as diabetes. Ultimately, insulin subcutaneous injection is the most effective treatment for diabetic patients. However, most patients must self-administer insulin at least twice daily for the rest of their lives, as this form of administration is frequently uncomfortable and inconvenient. Infections, insulin precipitation, lipoatrophy, or lipohypertrophy are commonly observed at the injection site. To date, nasal, pulmonary, and oral methods of insulin administration have been explored. Although insulin stimulation is the ideal method for diabetic patients, there are several obstacles to overcome, such as rapid insulin degradation in the stomach and limited oral bioavailability. Various strategies have been approved to improve these parameters, including the use of enzyme inhibitors, mucoadhesive polymeric agents, absorption-enhancing agents, and chemical modifications. Insulin-loaded nanocarriers can bypass numerous physiological limitations. The current review discusses the approach of nanotechnology in nose-to-brain delivery of nanoparticles for diabetes management.

Keywords Diabetes, Mucoadhesive, Nanoparticles, Nose to brain

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INTRODUCTION

Diabetes mellitus (DM), a widely prevalent chronic metabolic condition, is characterized by an elevation in blood glucose level or hyperglycaemia. Predominantly, it presents in two primary forms, referred to as type 1 and type 2. [1] Type 1 diabetes mellitus (T1DM) occurs when the body's immune system destroys pancreatic beta cells, the only cells capable of producing the insulin necessary to maintain normal blood sugar levels, [2] and is usually reported in children and young adults. [3] The pathophysiology of DM involves plasma concentrations of blood glucose signalling the central nervous system (CNS) to mobilize

energy reserves. [4], [5] Cerebral blood flow and tissue integrity, arterial plasma glucose, the rate at which plasma glucose concentrations decrease, and other existing metabolic fuels play a role. [6,7] In healthy individuals, the pancreas releases glucagon and insulin into the bloodstream to regulate glucose levels in the body. [8] Insulin enables glucose to enter body cells, where it is processed, thereby lowering blood sugar levels. [9] If blood glucose levels fall too low, the pancreas automatically releases glucagon to stimulate the liver to release glucose. After eating, amino acids and glucose are quickly absorbed into the bloodstream, causing an immediate increase in blood glucose levels. [10] This increase signals pancreatic beta cells to release insulin, which peaks about 20 minutes after eating. [11]

Patients with T1DM require insulin administration via injection or pump to survive. [3,12] Currently, T1DM or insulin-dependent diabetic individuals are routinely treated with periodic subcutaneous injections of insulin. This administration route is associated with significant discomfort, distress, and local infection risk, leading to low patient compliance. [13] Accordingly, due to poor patient compliance with injections, maintaining constant blood glucose levels is often difficult. [14]

Insulin, being proteinaceous in nature, its oral administration has numerous biological limitations. Multiple daily insulin injections are the most common treatment for T1DM globally. [15] Various carriers, such as macromolecules and liposomes, are used for in vivo drug delivery. The bioavailability in oral route delivery of insulin has been enhanced using strategies like enteric coating, enzyme inhibition, and absorption-enhancing substances. [16–18] additionally, nanoparticles are proposed as insulin carriers to improve the physicochemical stability of loaded insulin and thereby enhance its bioavailability. [19,20] The potential absorption mechanism of insulin-loaded nanoparticles through the intestine is explored. Natural polymeric materials like chitosan and its derivatives, alginate analogues, γ-PGA-based materials, and starch-containing nanoparticles have been employed for drug delivery systems designed for oral administration of insulin. [21,22] Therefore, the next generation of TIDM treatments may improve the quality of life for diabetic patients who regularly administer subcutaneous insulin injections.

In this review, novel insulin delivery methods based on nanoparticles, including dextran-insulin, solid-liquid insulin nanoparticles, and chitosan-insulin nanoparticles are presented and discussed.

MANAGEMENT OF DIABETES

The management of diabetes in children presents a significant challenge due to the scarcity of information on effective strategies. The optimal approach entails primary prevention, with lifestyle management serving as the safest and most prevalent treatment method. [23] In light of the alarming rise in diabetes cases among young individuals, there is an urgent demand for the development of more efficacious and secure anti-diabetic medications. [2,24] Although insulin demonstrates remarkable effectiveness in reducing blood sugar

levels, its administration via injection and the associated risk of hypoglycemia render it a less preferable initial choice. [24] Recent literature recommends a multidisciplinary team approach to address childhood diabetes, involving physicians, diabetes educators, nutritionists, and social workers. [25] Exercise, dietary adjustments, and weight management constitute crucial elements of diabetes control. [26]

A significant number of children necessitate lifestyle modifications and pharmacological intervention to regulate their blood sugar levels. [27–30] For patients with T1DM experiencing elevated HbA_1c levels due to chronic renal disease, metformin proves particularly beneficial. [31–33]

INTRANASAL ROUTE OF DRUG ADMINISTRATION

The intranasal (IN) route is commonly employed for local applications such as allergies and nasal congestion. Over the past few decades, the IN route has emerged as a prominent area of study for drug delivery across the central nervous system (CNS). [33–35] The olfactory neuroepithelium, found inside the nose, is the only body part that directly connects the external environment with the CNS, making it an ideal target for therapeutic interventions. [36] The IN route offers advantages such as safety, speed, non-invasiveness, and convenience. Furthermore, it enhances bioavailability, circumvents first-pass metabolism, and protects against drug degradation in the gastrointestinal (GI) tract. [37]

However, the IN route also has some drawbacks, including difficulties in administration for those with nasal congestion due to colds or allergies and its suitability restricted to potent drugs, as only limited amounts can be applied into the nasal cavity. [38] The delivery of materials from the nasal cavity to the CNS may occur via the paracellular pathway involving the olfactory neuroepithelium. This pathway is slow, passive, and suitable for transporting hydrophilic drugs, with its rate dependent on the drug's molecular weight. [39]

Insulin, a polypeptide hormone, is secreted by the pancreatic islet of Langerhans' beta cells. [40] As a key regulator of intermediary metabolism, insulin significantly impacts carbohydrate, lipid, protein, and mineral metabolism. [41] The IN route is being investigated for its accessibility, absorption surface area, and vascularity. Oral administration is the most straightforward route for nutrient absorption, with the gut offering the largest absorption surface of all routes, thus ensuring better efficacy. [42–44] Nanoparticles have gained interest for their ability to protect insulin from the stomach's highly acidic environment and enzymatic degradation. Their high surface area-to-volume ratio increases the bioavailability of the administered drug. [45]

To address the challenges associated with the parenteral administration of insulin, several nanotechnology-based strategies have been developed to enhance the intestinal absorption of peptides and proteins. [46] Biodegradable polymers such as chitosan, alginates, and dextran sulfates are commonly used to prepare insulin nanoparticles. [47]

POLYMERS FOR DRUG DELIVERY

Polymers, known for their biodegradable, non-toxic, and biocompatible properties, have emerged as popular carriers for insulin delivery. For instance, chitosan is the most commonly used material due to its favorable biological characteristics and ease of chemical modification. [48]

Chitosan, a common copolymer of beta-linked N-acetyl glucosamine, is naturally found in the shells of crustaceans such as shrimp, crabs, and lobsters, as well as in some fungi. Carboxylated chitosan and polymethyl methacrylate have been combined to create insulin-loaded nanoparticles to enhance insulin administration via the oral route. [49] When diabetic rats are administered insulin-containing nanoparticles (25, 50, or 100 IU per kg) orally, a reduction in their blood sugar levels is observed. [50,51]

Researchers have investigated and demonstrated improved glycemic status using nanoparticles made from various materials, including poly(lactide-co-glycolide) or PLGA, [52] poly-lactide acid (PLA), [53] polycaprolactone (PCL), [54] and lipidic polymers (solid-lipid NPs). [55]

The nasal administration of insulin has gained significant attention as an effective route for the systemic delivery of insulin. [56] The pharmacokinetic profile of intranasal insulin mimics the pulsatile pattern of endogenous insulin secretion in healthy volunteers during meals. The nasal cavity's numerous microvilli and highly vascular structure aid in preventing first-pass metabolism and enzymatic breakdown in the gastrointestinal tract, providing a large surface area (150 cm^2) for absorption. Despite the challenges posed by macrociliary clearance of formulations from the nasal cavity and the reduced permeability of the nasal mucosa to macromolecules, researchers have explored various enhancers to overcome these obstacles, including sodium lauryl sulfate, cyclodextrins, chitosan, laureth-9, phospholipids, bile salts, their derivatives, and enzyme inhibitors. [57–59]

Direct drug delivery to the brain is ideal for medications acting on the central nervous system (CNS). However, due to capillary endothelial cells, the blood-brain barrier only permits a limited number of drugs to cross. Therefore, novel approaches must be investigated. [60] Intranasal administration of molecules is known to reach the brain, suggesting that substances administered intranasally could be transported to the brain via a nose-to-brain route. [55,61]

DISCUSSION

The nasal-to-brain drug delivery route, which primarily utilizes the olfactory channel instead of systemic circulation, is advantageous and appealing for local drug delivery to the brain. [62] Although intranasal (IN) insulin has shown increased effectiveness in managing hyperglycemia in diabetics, its exact mode of action remains unclear. [63] The transport of small molecules, peptides, and proteins through the olfactory epithelium and along

olfactory and trigeminal nerve pathways from the nasal cavity to the brain is well documented and clinically recognized for CNS-active drugs like sumatriptan, oxytocin, or insulin. Insulin, a biopharmaceutical with extensive clinical research, has evolved into a crucial regulatory hormone in the central brain system (CNS). [64]

Insulin receptors are predominantly located in synapses within the hippocampus, frontal cortex, and entorhinal cortex, where insulin signaling promotes synaptogenesis and synaptic remodeling. [65] Abnormalities in brain insulin metabolism and insulin resistance have been linked to various CNS disorders, including Alzheimer's disease, depression, [66–68] autism, [69] schizophrenia, [70] Huntington's disease, [71] Parkinson's disease [72]. IN insulin has been shown to improve memory, brain metabolic health, and moderate cognitive impairment in patients with Alzheimer's disease. [73]

In a study by Craft et al., the effects of intranasal insulin delivery on cognitive and functional outcomes were examined. [74] This study used a nasal drug delivery system to administer insulin intranasally for four months at doses of 20 or 40 IU. [75] The recommended amount can be provided by inhaling the insulin concentration released by this device into a chamber covering the patient's nose for two minutes. The results indicated that IN insulin infusion improved delayed memory compared to the placebo, suggesting that IN insulin may be beneficial for individuals with Alzheimer's disease. [76–78]

CONCLUSIONS

Polymeric nanoparticles have attracted significant attention over the past few years, with a focus on various insulin delivery routes. In the intranasal route of administration, insulin is combined with nanoparticle formulations to prevent its degradation and enhance its absorption in the nasal cavity. Polymeric nanoparticles for insulin delivery pathways appear to be a more promising alternative compared to other methods. However, further research is needed in this field to achieve the goal that has eluded researchers for many years.

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DECLARATIONS

Authors' contributions

ARS and PGM collected the reference material and prepared the draft of manuscript. ARS and MRK conceptualized, designed, and concluded the work and prepared the final version for submission. The authors read and approved the final manuscript before publication.

Conflict of interest

Theauthors declare that they have no potential conflicts of interest.

Data availability

The data that support the findings of this study are available on request from the corresponding author, ASN.

Ethical approvals

Not applicable.

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